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| 09/817,913 | 08/06/2001 | Zuomei Li | MET-021US1 | 8110 |

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| EXAMINER | |
|---|---|
| VAKILI, ZOHREH | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/817,913 | LI ET AL. | |
| | Examiner | Art Unit | |
| | ZOHREH VAKILI | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *45-48,50,51,53 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-48,50,51,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

**Claims 45-48, 50-51, and 53-54 are presented for examination.**

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's submission filed December 18, 2008 has been received and entered into the present application. Claims 45-48, 50-51, and 53-54 are pending and are herein examined on the merits.

**LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:**

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a method for modulating cell proliferation of a cell comprising inhibiting specific histone deacetylase (HDAC) isoforms that is involved in cell proliferation with an agent that inhibits one or more specific deactylase isoforms,

which meet the written description and enablement provisions of 35 USC 112, first paragraph.

However, claims 45-48, 50-51, and 53-54 are directed to encompass small molecule inhibitor, which only correspond in some undefined way to specifically instantly disclosed agent. None of these small molecule inhibitor, meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*. (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of the above specifically disclosed agent, the skilled artisan cannot envision the detailed chemical structure of the encompassed small molecule inhibitor, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) Baird, 30

USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> …To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above agent, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115).

***Claim Rejections - 35 USC § 112, 2nd Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47, 48, 53, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claims 47, 48, 53, and 54 is lacking clear antecedent basis regarding which isoform is meant regarding instant claims 47, 48, 53, and 54 because independent claims 45 and 50 from which they depend directly or indirectly indicate isoforms that are inhibited as well as isoforms not being inhibited.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 45-48 are rejected under 35 U.S.C. 102(b) as anticipated by Jones et al. (Nature Genetics, 1998, of record).

Claim 45 is directed to a method of modulating cell proliferation in a cell comprising the step of contacting the cell with an agent that inhibits one or more histone deacetylase isoforms. Claims 46-48 limit claim 45 to proliferation that is neoplasia and recite specific histone deacetylase isoforms.

Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase. Jones et al. do not explicitly state that proliferation of the cells is inhibited, but the method of Jones et al. comprises all of the steps of the claimed method and, absent evidence to the contrary, would be expected to inhibit proliferation, including neoplastic proliferation.

Thus, Jones et al. disclose all limitations of and anticipate claims 45-48.

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361).

Kwon et al. disclose a small molecule inhibitor which inhibits **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54), which has the effect of inducing the reversion of cells transformed with a known oncogene from the morphology of a transformed cell to that of a normal cell.

Thus, Kwon et al. disclose all limitations of and anticipate claims 45-48, 50-51, and 53-54.

Claims 45-48 are rejected under 35 U.S.C. 102(e) as being anticipated by MacLeod et al. (US 2003/0078216).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim 45 is directed to methods of inhibiting cell differentiation or proliferation, including neoplastic cell proliferation in an animal, by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms.

MacLeod et al. disclose a method of inhibiting cell proliferation by inhibiting histone deacetlyase using antisense oligonucleotides. MacLeod et al. further disclose that the antisense oligonucleotides are targeted to the histone deacetylase isoforms recited in claim 47 and that the method may be performed in humans.

Thus, MacLeod et al. disclose all limitations of and anticipate claims 45-48.

Claims 45-48, 50-51, and 53-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361).

Kwon et al. disclose a small molecule inhibitor which inhibits **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54), which has the effect of

inducing the reversion of cells transformed with a known oncogene from the morphology of a transformed cell to that of a normal cell.

Thus, Kwon et al. disclose all limitations of and anticipate claims 45-48, 50-51, and 53-54.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sambucetti et al. (Journal of Biological Chemistry 1999, vol. 274, pages 34940-34947), Taunton et al. (Science 1996, cited on IDS), Baracchini et al. (US 5,801,154) and Bennett et al. (US 5,998,148).

Claim 45 are directed to methods of inhibiting cell differentiation or proliferation by administering an agent that inhibits one or more specific histone deacetylase isoforms. Claims 46-48 limit claim 45 to neoplastic cell proliferation and recite specific histone deacetylase isoforms.

Sambucetti et al. teach that inhibition of histone deacetylase using the tetrapeptide inhibitor TPX inhibits tumor cell proliferation. Sambucetti et al. do not teach the use of antisense oligonucleotide inhibitors of histone deacetylase.

Taunton et al. teach the isolation and sequence of **histone deacetylase-I (HDAC-1)** (as recited in claims 47-48 and 53-54).

Baracchini et al. teach that antisense oligonucleotides can be used for research purposes, and also teach that preferred antisense oligonucleotides are modified in their sugar, backbone linkage and nucleobase composition (col. 6). Baracchini teaches that such modifications are desirable in antisense oligos because these modifications have desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases. Baracchini et al provide specific embodiments of such modifications at columns 6-8 and in Example 1. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture.

Table 1 exemplifies the successful practice of general antisense design taught at columns 8- 10. Column 4 teaches various carriers for antisense delivery. Baracchini et al. also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett et al. are considered to parallel those of Baracchini et al. Bennett et al. teaches general antisense targeting guidelines at columns 3-4. Bennett et al. also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 6-7 teach that preferred antisense oligonucleotides contain modified internucleoside linkages including phosphorothioate linkages, among others. Columns 7-8 teach that preferred antisense oligonucleotides comprise modified sugar moieties including 2'-O-methoxyethyl. Bennett et al. also teach one of ordinary skill to modify nucleobases in antisense oligonucleotides, including the teaching of 5-methylcytosine (col. 8-9), and also to use chimeric antisense oligonucleotides (col. 9-10). Bennett et al. teach that the above modifications are known in the art to provide beneficial attributes to antisense oligonucleotides such as increased hybridization and nuclease protection, for example. Columns 10-24 teach numerous carriers for antisense oligonucleotides. Table 1 teaches the successful

targeting of those regions taught in columns 3-4 with chimeric phosphorothioate oligonucleotides having 2'-MOE (a 2'-O-methoxyethyl modification). Thus, Bennett et al. is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

It would have been obvious to one of ordinary skill in the art to use the cDNA sequence taught by Taunton et al. to generate antisense sequences as taught by Baracchini and Bennett for inhibition of **histone deacetylase-I** expression for the purposes of treating neoplastic cells via inhibition of **histone deacetylase-1 as taught by Sambucetti et al**. One would have been motivated to create such compounds because Sambucetti et al. teach that their inhibitor of histone deacetylase can be used to inhibit tumor cell proliferation. Furthermore, both Bennett and Baracchini et al. teach that antisense molecules can be easily made and used to inhibit any target so long as the sequence is known, and provide for their methods of use in humans. Therefore, one of ordinary skill in the art would have been motivated to use the sequence histone deacetylase of Taunton et al. to develop antisense inhibitors for the purpose of treating neoplastic cells, because Sambucetti et al. teach that inhibition of **histone deacetylase-I (HDAC-1)** can inhibit tumor cell proliferation.

Finally, one would have a reasonable expectation of success given that Baracchini et al. and Bennett et al. provide a detailed blueprint for making and using modified antisense compounds targeted to a target gene, the sequence of which is provided by Taunton, and the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention of claims 45-48 would have been prima facie obvious as a whole to one of ordinary skill in the art at the time the invention was made.

***Response to Argument***

Applicant's remarks have been fully and carefully considered in their entirety, but fail to be persuasive.

Specification does not define or give any example as what the Applicant is referring to as small molecule inhibitors. The specification clearly states that the agents used to perform the claimed method include antisense oligonucleotides and small molecule inhibitors. Since, it appears that the Applicants were not in possession of small molecule inhibtors, Examiner has interpreted the invention as being limited to including antisense oligonucleotides as the agent.

Applicant's amendments and remarks have been carefully considered in their entirety, but fail to be persuasive in establishing error in the propriety of the present rejection.

**Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner March 17, 2009
1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614